REMARKS

Claims 1-18 and 21-24 are pending in the application. Claims 19 and 20 have been cancelled.

Claims 1-18 and 21 have been amended. Initially, applicants note the correction of "cyclising" in Claim 1, "hydrolysable" in claim 2, and "cyclisation" in claims 8, 9, and 18 to "cyclizing," to "hydrolyzable" and "cyclization" respectively, in conformation with standard American spelling. Additionally, in Claim 1, the phrase "which includes the step of cyclizing" has been replaced with "comprising the step of cyclizing." The change was made in the interest of clarity and does not narrow the claimed subject matter. Support for the amended claim language "comprising cyclizing..." is found throughout the specification and particularly at page 14-15.

Further, Claim 1 has been amended by rephrasing the definition of R^3 to indicate more clearly that CO_2R^3 is an actual or a protected carboxyl group. This rephrasing omits the possibility that CO_2R^3 is a carboxylate salt; however, this possibility is retained in the claim and is denoted by the phrase added at the end of Claim 1, "and optionally forming the carboxylate salt of said compound..." Therefore, these changes do not narrow the subject matter of Claim 1. Additionally, the phrase "and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent" has been deleted. No new matter has been added.

Additionally, in accordance with proper dependent claim form, and without thereby limiting the scope of the claimed invention, Claims 2 – 18 have been amended to recite "The process according to Claim 1," rather than "A process according to Claim 1."

In Claim 2, the definition of CO_2R^5 has been amended to conform with the corresponding phrase in Claim 1, hereinabove explained. Again, no new matter is added by this amendment. Support for the inclusion of carboxylate salts within the definition of CO_2R^5 in Claim 2 is found in the specification at page 5, line 25 to page 6, line 4, for example. No new matter has been added.

Additionally, Claims 4, 5, 7-11, 13, 15, and 18 have been amended to comply with the requirements of 37 C.F.R. 1.75(c) that a multiple dependent claim may not depend on another multiple dependent claim. No new matter has been added.

Additionally, Claims 11 and 18 have been amended to include certain reaction steps, instead of the term "converting." Support for the amendment to Claims 11 and 18 is found throughout the specification and particularly at page 11, line 16, to page 15, line 12. No new matter has been added.

Additionally, and in an effort to define the invention to which applicants are entitled, the subject matter of Claim 17 has been separated into two claims, amended Claim 17 and new Claim 24. Support for Claim 24 is found throughout the specification and in original Claim 17.

Additionally, regarding Claim 21, compound IIB has been deleted, and the remaining subject matter of Claim 21 has been separated into three Claims, namely amended Claim 21 and new Claims 22 and 23. Compound IIB is deleted without prejudice, solely in an effort to advance the prosecution of the present application. Applicants reserve the right to pursue this subject matter in a continuing application.

Applicants wish to bring to the Examiner's attention the addition of new Claims 22-24. Claims 22 and 23 are directed to subject matter removed from Claim 21, as

indicated hereinabove. Claim 24 is directed to subject matter removed from Claim 17. No new matter has been added.

In the Office Action, Claim 21 has been rejected under 35 U.S.C. §102(b), as allegedly anticipated by WO 92/01696 or Elliott et al., *J. Org. Chem.* 1996, 62, 4998-5016 (hereinafter "Elliott et al."). Also, Claims 20 and 21 have been rejected under 35 U.S.C. §102(b), as allegedly anticipated by WO 92/01969 or 93/25551 or WO 96/17847.

Additionally, the Examiner has rejected Claims 1-21 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner has also rejected Claims 1-20 under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support for R^4 = Cl or OH, as well as for R^4 = alkyl substituted with Cl or OH. Claims 1-21 have been rejected under 35 U.S.C. §112, paragraphs 1 and 2, as allegedly failing to describe the claimed invention in sufficiently full, clear, and exact terms as to enable any person skilled in the art to make and use the invention.

The Examiner has objected to Claims 4-20 under 37 C.F.R. 1.75(c), as allegedly in improper form. Additionally, the Examiner has objected to Claim 2 under 37 C.F.R. 1.75(c), as allegedly in improper dependent form.

This response addresses each of the Examiner's rejections. Accordingly, the present application is in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

The Examiner has rejected Claim 21 under 35 U.S.C. §102(b), as allegedly anticipated by WO 92/01696 or Elliott et al. Also, Claims 20 and 21 have been rejected under 35 U.S.C. §102(b), as allegedly anticipated by WO 92/01969 or 93/25551 or WO 96/17847.

The Examiner has alleged that compound IIB is disclosed in Example 11 of WO 92/01696 and in Example 12 of Elliott et al. Accordingly, and in an effort to favorably advance the prosecution of the present application, applicants have amended Claim 21 to omit compound IIB. Applicants reserve the right to pursue the subject matter directed to compound IIB in one or more continuing applications.

Also, Claims 20 and 21 have been rejected under 35 U.S.C. §102(b), as allegedly anticipated by WO 92/01696 or 93/25551 or WO 96/17847. Applicants initially note that, in an effort to favorably advance the prosecution of the present application, and without prejudice, applicants have hereinabove cancelled Claim 20. Applicants reserve the right to pursue the subject matter of Claim 20 in one or more continuing applications.

Additionally, applicants note that Claim 21 has been amended and now includes only compounds III, IIIA, and VIII, none of which include the tetrahydrofuranyl ring at position 3. Applicants reserve the right to pursue the subject matter of Formula IIB in one or more continuing applications. With respect to amended Claim 21, applicants respectfully traverse this rejection. Directing the Examiner's attention to Example 11 of WO 92/01696, applicants respectfully submit that the final product of Example 11 of WO 92/01696 is diphenylmethyl (6R,7R)-7-phenylacetamido-3-[(RS) - tetrahydrofuran-2-yl] ceph-3-em-4-carboxylate, which differs from compound III in that Example 11 has a tetrahydrofuran ring at position 3, whereas, by contrast, compound III of the present application lacks a tetrahydrofuran ring and instead includes a straight-chain dihydroxyalkyl group at position 3.

Regarding WO 96/17847 and WO 93/25551, applicants respectfully submit that all products and starting materials in WO 96/17847 and WO 93/25551 contain the tetrahydrofuran ring at position 3. By contrast, the present invention provides a synthetic

method for cephalosporin compounds which comprises cyclization of an alkyl group at position 3 to form the tetrahydrofuran (m = 1) or tetrahydropyran (m =2) ring. Compound III is an intermediate in this method.

Accordingly, the rejection based on 35 U.S.C. §102(b) is overcome, and withdrawal thereof is respectfully requested.

Additionally, the Examiner has rejected Claims 1-21 under 35 U.S.C. §112, first paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In this regard the Examiner has alleged that the term "acyl" is indefinite and suggests that acids of sulfur, phosphorus, and arsenic might also be embraced by the term "acyl." In response, applicants respectfully direct the standard chemical reference work Hawley's Condensed Chemical Dictionary, 12th ed., Richard J. Lewis, Sr., ed., New York, Van Nostrand Reinhold, 1993, ISBN 0-442-01131-8, at pages 21-22 (copy attached hereto as Exhibit A), wherein the term "acyl" is defined as "[a]n organic group in which the OH of the carboxyl group is replaced by some other substituent (RCO-). Examples: acetyl CH_3CO, benzoyl C_6H_5CO." Applicants respectfully submit that a person skilled in the art would understand the term "acyl" to have the meaning provided in this reference.

Additionally, the Examiner has alleged that the term "easily removable" is indefinite and asks how one could distinguish between protecting groups that are easily removable and those which are not easily removable. In response, applicants initially note that the phrase used in original Claim 1 was not "easily removable" but "readily removable." Applicants further note that Claim 1 has been amended by omitting the phrase "readily removable."

Additionally, the Examiner has alleged that the phrasing of "which includes the step of cyclizing" is unclear. The Examiner questions the timing of the cyclization step (i.e., formation of the tetrahydrofuranyl moiety) relative to other steps in the reaction sequence. In response, applicants note that Claim 1 has been amended to omit the language of "which includes the step of cyclizing." Support for the amended claim language "comprising cyclizing..." is found in the specification at page 14-15. No new matter has been added.

Additionally, the Examiner has queried whether in Claim 1 "R^4 alkyl" is intended to be "R^4 = alkyl." In response, applicants note that Claim 1 has been amended to omit the clause in which "R^4 alkyl" occurs.

Additionally, the Examiner has alleged that the term "converting" in Claims 11 and 18 is indefinite and unduly functional and that this term fails to recite a specific reaction step. In response, applicants note that Claims 11 and 18 have been amended to include certain reaction steps.

Additionally, the Examiner has alleged that Claim 12 is indefinite because of the inclusion of both isomers. Accordingly, in an effort to favorably advance the prosecution of the present application, Claim 12 has been hereinabove amended to omit structure VIIIB.

Additionally, the Examiner has alleged that the dependence of Claim 15 on Claim 11 makes no sense, because Claim 11 does not teach a particular configuration. In response, applicants note that Claim 15 has been amended to depend from Claim 12, which teaches the isomer in which the carbon attached to position 3 of the cephalosporin nucleus has the "S" configuration.

Additionally, the Examiner has alleged that the use of "pinacol" in Claim 17 is in error. The Examiner alleges that the pinacol boronate cannot be formed from the variable choices listed later in the claim. The Examiner further alleges that the use of "pinacol" makes Claim 17 improperly dependent on Claim 16. In response, applicants note that Claim 17, as amended, directed only to the process wherein the group Z is a pinacol boronate group. New claim 24 is directed to the process wherein the group Z is a tartrate boronate group.

The Examiner has stated that Claim 21 must set forth what the claimed compounds actually are. In response, the structure of the three compounds have been provided.

Accordingly, the rejections under 35 U.S.C. § 112, second paragraph, are overcome, and withdrawal thereof is respectfully requested.

Further, the Examiner has rejected Claims 1-20 under 35 U.S.C. §112, first paragraph, alleging that the specification does not reasonably provide enablement for R_4 = Cl or OH or for R_4 = alkyl substituted by Cl or OH. Applicants respectfully traverse this rejection. Initially, applicants respectfully direct the Examiner's attention to page 9, line 24-31, of the specification, wherein the cyclization methods are discussed. Applicants note that the specification teaches that cyclization may be carried out by a variety of methods and conditions, namely under acid catalysis or by treatment with an acylating agent in the presence of an amine. Applicants respectfully submit that a person of ordinary skill in the art would choose a method of cyclization that would be appropriate for the substituents present. For example, it is well-known in the art that under acidic conditions the hydroxyl group is in equilibrium with a protonated form, the hydronium ion. It is likewise well-known that the protonated hydroxyl group is a better leaving group that chloride ion. Therefore, a person of

ordinary skill in the art would employ acidic conditions for cyclization of a compound III in which R^4 is Cl or alkyl with a Cl substitutent. Similarly, a person of ordinary skill in the art would know that a hydroxy group on R^4 would require protection during reaction steps with very strong bases, such as Grignard reagents. In summary, then, applicants respectfully submit that, contrary to the Examiner's allegation, the specification does indeed enable a person skilled in the art to practice the invention as claimed without undue experimentation. Thus, the rejection under 35 U.S.C. § 112, first paragraph, is overcome, and withdrawal thereof in respectfully requested.

Additionally, the Examiner has rejected Claims 1-21 under 35 U.S.C. §112, paragraphs 1 and 2, as allegedly failing to describe the claimed invention in sufficiently full, clear, and exact terms as to enable any person skilled in the art to make and use the invention. The Examiner has alleged that the molecule is depicted as having a negative charge and as lacking an accompanying counter ion. In response, applicants note initially that Claim 1 has been amended so as to clarify the phrase to which the Examiner refers. Claim 1, as amended, now provides that the compound may be a carboxylic acid, a protected carboxylic acid, or a carboxylic acid salt. Accordingly the rejection under 35 U.S.C. § 112, paragraphs 1 and 2 is overcome, and withdrawal thereof is respectfully requested.

The Examiner has also objected to Claims 4-20 under 37 C.F.R. §1.75(c) as allegedly being in improper form. Applicants note that these claims have been corrected to display proper form. Therefore, withdrawal of the objection is respectfully requested.

Additionally, the Examiner has objected to Claim 2 under 37 C.F.R. §1.75(c) as allegedly in improper dependent form with respect to Claim 1, on which it depends.

Applicants have hereinabove amended Claim 2 to conform with formal requirements. Therefore, withdrawal of the object is respectfully requested.

Lastly, the Examiner has stated that the title of the invention is not descriptive. Therefore, the title has been changed to one that describes the invention more specifically.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Thus, in view of the forgoing amendments and remarks, the present application is in condition for allowance.

Respectfully submitted,

Peter I. Bernstein
Registration No. 43,497

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
(516) 742-4343

HLR/PIB:lf

"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

IN THE SPECIFICATION:

Please replace the title of the invention with the following title:

A NOVEL PROCESS FOR THE PREPARATION OF CEPHALOSPORIN COMPOUNDS AND SYNTHETIC INTERMEDIATES ~~NOVEL PROCESS~~

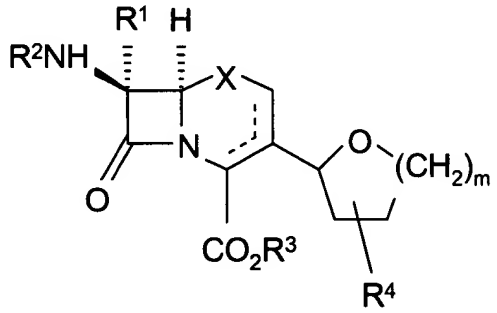
IN THE CLAIMS:

Please cancel Claims 19 and 20 without prejudice.

Please add Claims 22, 23, and 24 as follows:

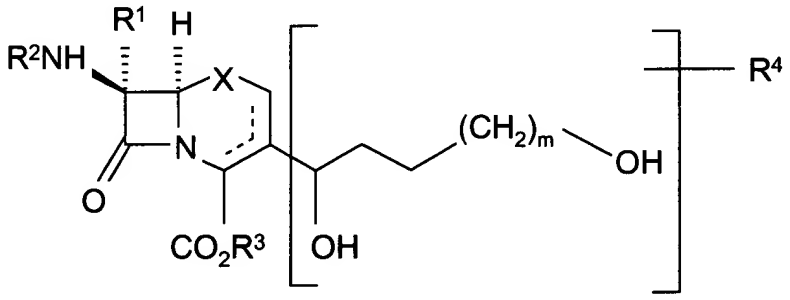
Please amend Claims 1-21 as follows:

1. (Amended) A process for the preparation of a compound of formula (II):



(II)

comprising ~~which includes the step of~~ cyclizing a compound of formula (III):

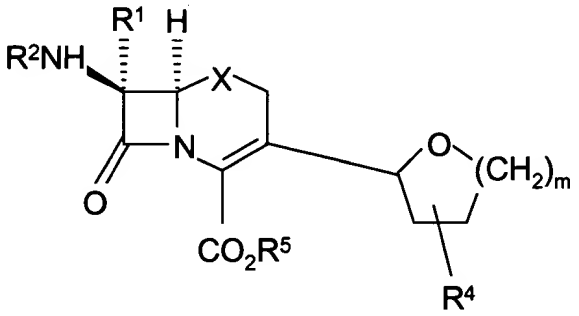


(III)

wherein in formulae (II) and (III), R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group; ~~CO_2R^3 is a carboxy group or a carboxylate anion, or salt or~~ R^3 is hydrogen or a ~~readily removable~~ carboxy protecting group; R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different ~~and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent~~; X is S, SO, SO_2, O, or CH_2; and m is 1 or 2; and the dotted line indicates that the compounds (II) and (III) may be a 2-cephem or a 3-cephem system, and where in formula (III) the substituent(s) R^4 when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain,

and optionally forming the carboxylate salt of said compound of formula III.

2. (Amended) The ~~A~~ process according to claim 1 wherein the compound of formula (II) is a 3-cephem of formula (IIA) or a pharmaceutically acceptable salt or pharmaceutically acceptable in vivo ~~hydrolysable~~ hydrolyzable ester thereof:



(IIA)

wherein R^1, R^2, R^4, m and X are as defined with respect to formula (III) and the group CO_2R^5 is CO_2R^3 where CO_2R^3 is a carboxyl group, a protected carboxyl group or a ~~carboxylate anion~~ carboxylic acid salt.

3. (Amended) ~~A~~ The process according to claim 1 or 2 wherein X is S, O, or CH_2.

4. (Amended) ~~A~~ The process according to ~~any one of~~ claims ~~1,~~ or 2 ~~or 3~~ wherein the cyclic ether at the 3-position of the cephalosporin nucleus in formulae (II) and (IIA) is unsubstituted.

5. (Amended) ~~A~~ The process according to ~~any one of~~ claims 1 ~~to 4~~ or 2 wherein m is 1, so that the cyclic ether at the 3-position in formulae (II) and (IIA) is a tetrahydrofuranyl system.

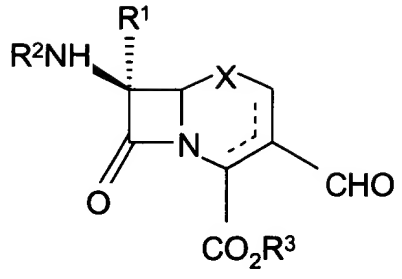
6. (Amended) ~~A~~ The process according to claim 5 wherein the cyclic ether at the 3-position in formulae (II) and (IIA) is an (S)-tetrahydrofuran-2-yl ring system.

7. (Amended) ~~A~~ The process according to ~~any one of the preceding~~ claims 1 or 2 wherein in formula (III) when m is 1 the 1, 4-dihydroxylbut-1-yl side chain is the less polar diastereoisomeric form.

8. (Amended) ~~A~~ The process according to ~~any one of the preceding~~ claims 1 or 2 wherein the cyclization ~~cyclisation~~ reaction of the process of the invention is carried out by treatment of the compounds (III) with an acid catalyst.

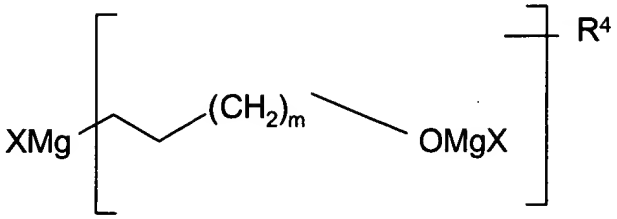
9. (Amended) ~~A~~ The process according to ~~any one of~~ claims 1 ~~to 7~~ or 2 wherein the cyclization ~~cyclization~~ reaction is carried out by treatment of the compounds (III) with an acylating agent.

10. (Amended) ~~A~~ The process according to ~~any one of the preceding~~ claims 1 or 2, wherein the compound of formula (III) is prepared by reacting a compound of formula (IV):



(IV)

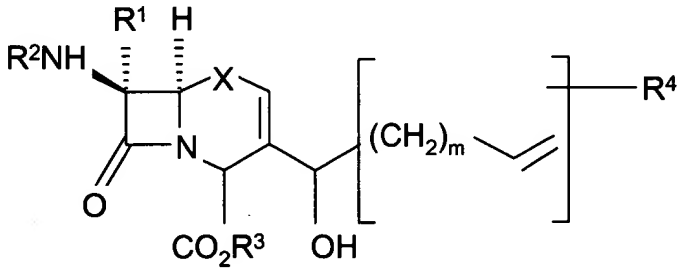
with a compound of formula (V):



(V)

where R^4 and m are as defined with respect to formula (III), and X and X^1 are the same or different halogen, and the dotted line in formula (IV) indicates that the compound (IV) may be a 2- or 3- cephem system.

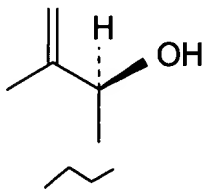
11. (Amended) ~~A~~ The process according to ~~any one of~~ claims 1 or 2 ~~to 10~~, wherein the compound of formula III is prepared by ~~converting~~ coupling a compound of formula (IV) (as defined in claim 10) ~~into~~ with an organometallic reagent to form a compound of formula (VIII):



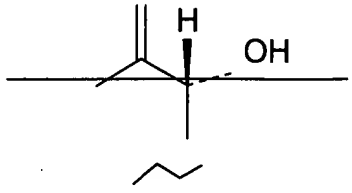
(VIII)

and wherein said compound of formula VIII is then hydroxylated to form a compound of formula III, where R^1, R^2, R^3, R^4, m, and X are as defined with respect to formula (III).

12. (Amended) ~~A~~ The process according to claim 11 wherein the compound of formula (VIII) has ~~a hydroxyl group~~ the configuration shown in (VIII A):



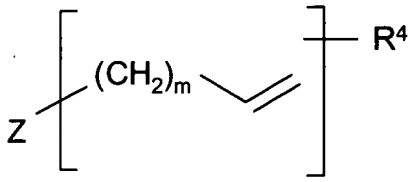
(VIII A)



(VIII B)

13. (Amended) ~~A~~ The process according to claim 12 wherein the compound of formula (IV) is formed into a compound of formula (VIII) by reaction with an organometallic reagent.

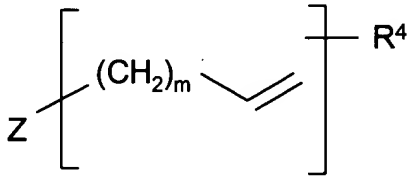
14. (Amended) ~~A~~ The process according to claim 13 wherein the organometallic reagent is a compound of formula (IX):



(IX)

where m and R^4 are as defined in formula (VIII), and Z is YMg where Y is a halogen.

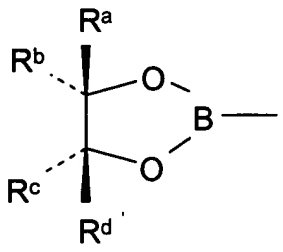
15. (Amended) ~~A~~ The process according to claim ~~11 or~~ 12 wherein the compound of formula (VIII) is prepared stereospecifically from a compound of formula (IV) by the use of a compound (IX):



(IX)

in which Z is a chirally inducing group which leads to preferential formation of a desired configuration of the hydroxyl group in the compound (VIII).

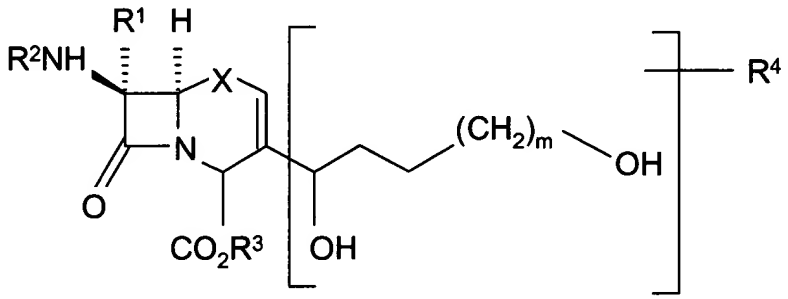
16. (Amended) ~~A~~ The process according to claim 15 wherein Z is the boronate group (X):



where R^a, R^b, R^c, and R^d are independently selected from hydrogen, alkyl and protected carboxy.

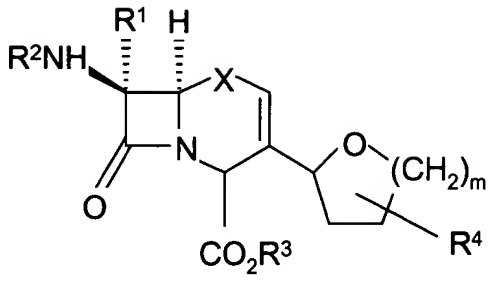
17. (Amended) ~~A~~ The process according to claim 16 wherein group (X) is a pinacol boronate group ~~or a tartrate boronate group wherein R^a is alkylcarboxylate, R^b is hydrogen, R^e is alkylcarboxylate and R^d is hydrogen~~.

18. (Amended) The process according to ~~any one of~~ claims 10 ~~to 17~~ wherein the compound (IV) is ~~converted into~~ alkylated with a compound of formula V to form a compound of formula VIII, which is then hydroxylated to form a 2-cephem compound of formula (III A):



(III A)

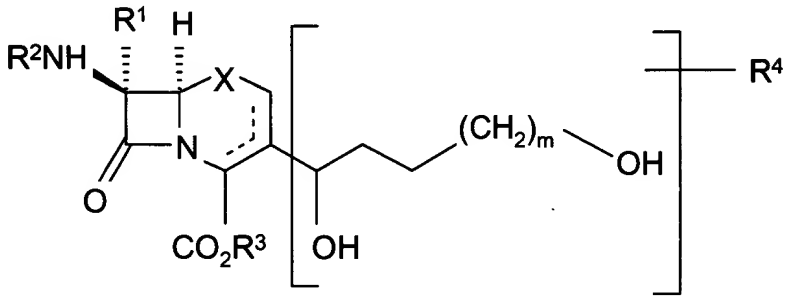
which is ~~converted during the cyclisation cyclization process of the invention into~~ then cyclized to form a 2-cephem compound of formula (II B):



(II B)

where R^1, R^2, R^3, R^4, X and m are as defined in formulae (II) and (III) above, and the 2-cephem (IIB) is then converted into a 3-cephem.

21. (Amended) A compound of formula ~~(IIB),~~ (III), ~~(IIIA) or (VIII)~~



(III)

wherein R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group; R^3 is hydrogen or a carboxy protecting group; R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different; X is S, SO, SO_2, O, or CH_2; and m is 1 or 2; and the dotted line indicates that the compound may be a 2-cephem or a 3-cephem system, and where the substituent(s) R^4 when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain.